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Examination Requested

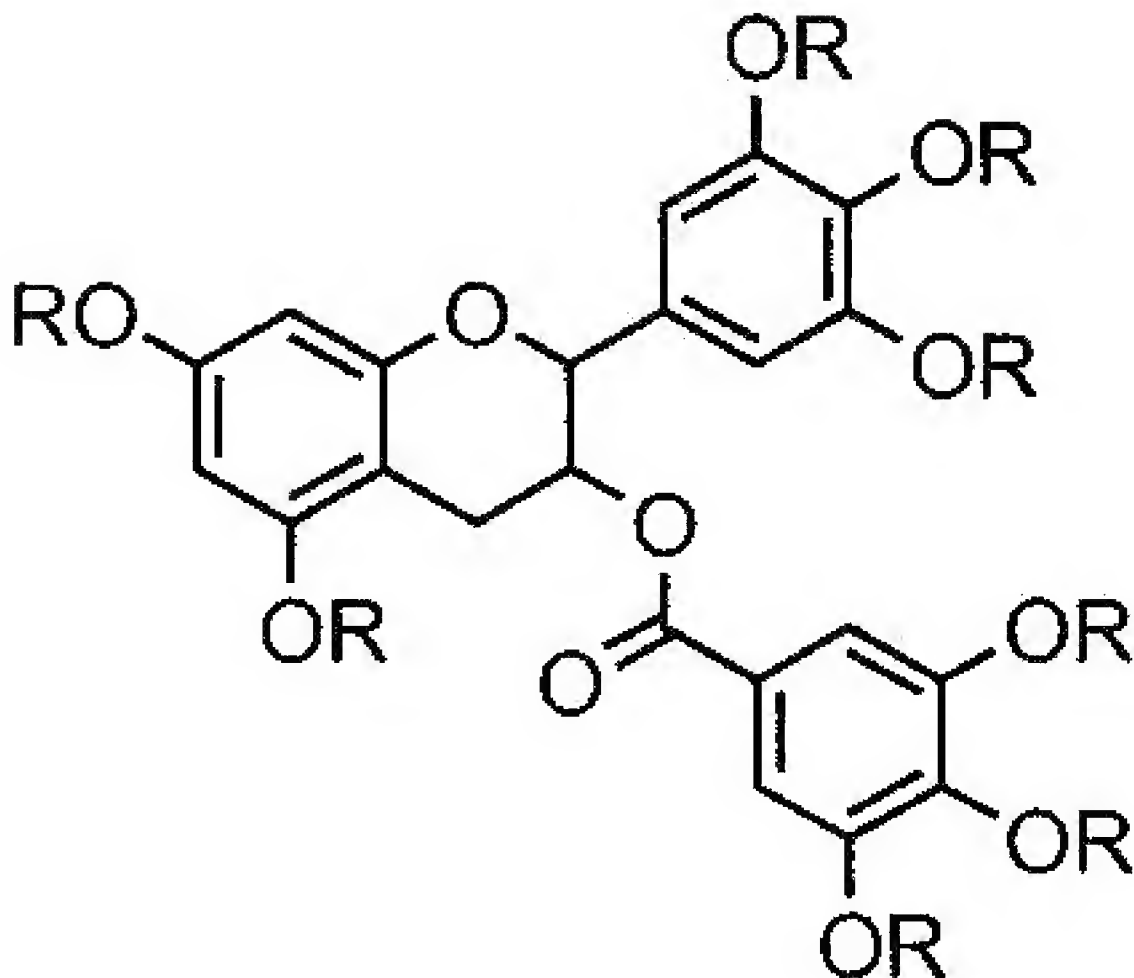
Title of Invention EGCG derivatives, Preparation method thereof and cosmetic composition containing thereof



Abstract

The invention relates to the epigallocatechin-3-gallate (hereinafter epigallocatechin-3-gallate "EGCG") derivative expressed in below chemical formula 1 and a method of manufacture thereof and the cosmetic composition containing this. And it characterizes to react EGCG and nicotinic acids to the equivalence ratio of 1:8~10.4 in presence of a coupling agent in the organic solvent and obtain the EGCG derivative.

[Chemical formula 1]



In the above case, R the nicotinoyl, and the isonicotinoyl or the picolinoyl.

As the EGCG derivative compound of the present invention is material having the effect that prevents the aging of the biological film the production of peroxide is controlled it controls the oxidizing action by the active oxygen in the skin in coating at in vivo and the effect promoting the collagen biosynthesis, , in addition the magnetic pole about the skin has no the spring plate multiplication of the skin, and prevention and improvement effect of the skin aging have.



#### Keyword(s)

The EGCG derivative, nicotinic acids, nicotinoyl, isonicotinoyl, picolinoyl.



#### Description

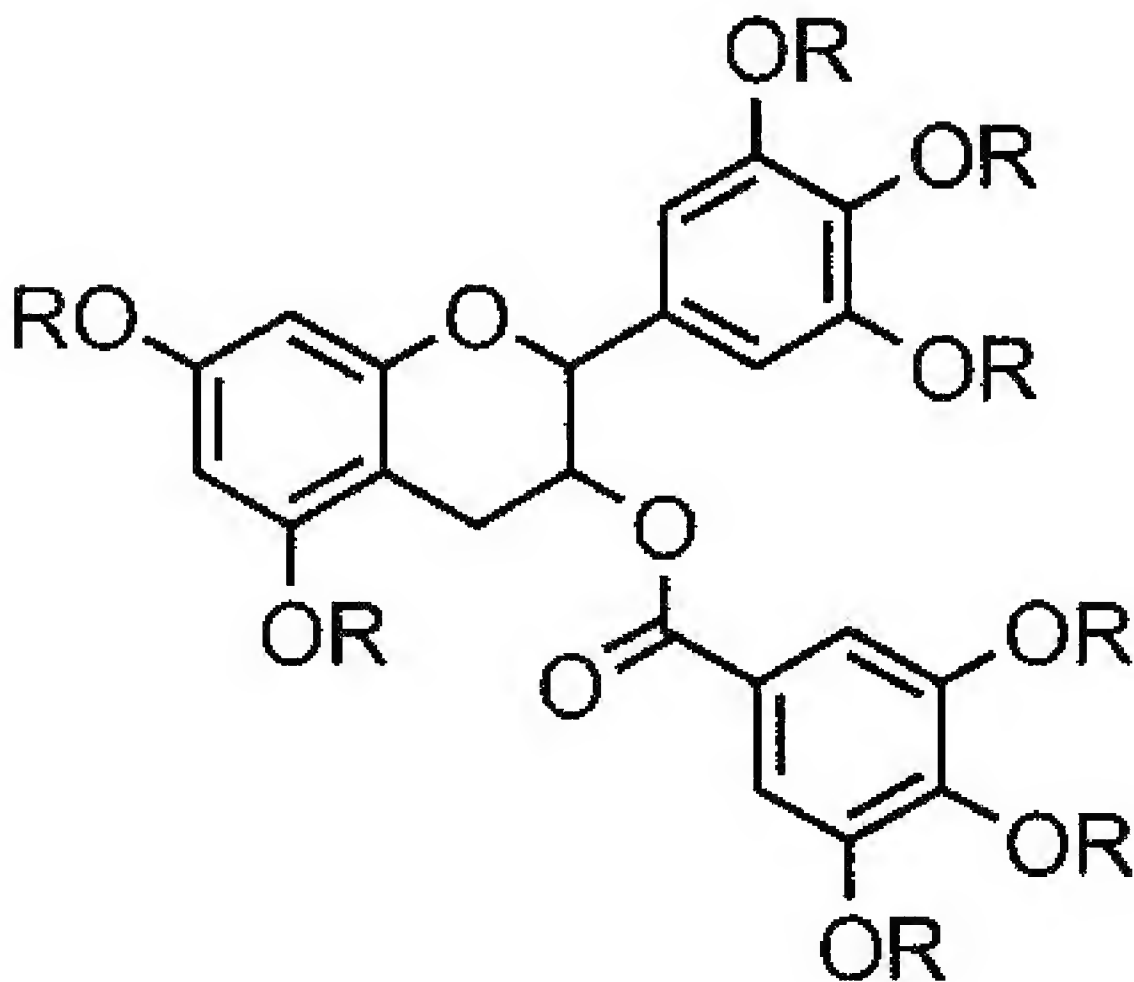
## ■ Details of the Invention

### ■ Purpose of the Invention

#### ■ The Technical Field to which the Invention belongs and the Prior Art in that Field

The invention relates to below chemical formula 1. And it is about the expressed epigallocatechin -3- gallate (hereinafter epigallocatechin-3-gallate "EGCG") derivative and a method of manufacture thereof and the cosmetic composition containing this.

[Chemical formula 1]



In the above case, R the nicotinoyl, and the isonicotinoyl or the picolinoyl.

(-) As the material which - epigallocatechin -3- gallate most very much exists among the catechin compound of the green tea, it is known as that the various effect is had and it has. Particularly, in the skin, it softened the inflammation, caused with UV-B the erythema, and the skin wife. The production of peroxide was obstructed. And with reducing the penetration of leukocyte it was reported. In EGCG due to the various effect is the food, and drug and cosmetic, many application studies had been being included.

But EGCG very unstables. And many thing which has been being restricted are fact due to the extreme hydrophilic property as to use. Particularly, it used as the toiletry raw material, it economiced, it yet \*\*\*ed and because the stabilization method was not developed, the application at the various field was not very much included due to the reason for being technical.

There can be the chemical method through the deformation to the physical method like the inclusion which a lot uses polymer and the derivative which is more stable as the method of the stabilization the thing having the method for stabilizing the effect firstly keeps EGCG is applied to cosmetic etc. and the property of matter in which use facilitates is necessary. Particularly, there can be the whole or the derivative which it partly substitutes to the alkyl group or the acyl radical -OH of 8 of EGCG as the example the chemical method at the same time could accomplish the improvement of the solubility and stabilization and it had been being very much studied, and concrete. But there can be the disadvantage that the harmful material thing same in the analysis at in vivo like the acetic acid or the benzoic acid becomes in case of the material substituted as the acyl radical which such compounds does not manufacture through the reaction which directly uses EGCG, but difficulty economically has to be general to obtain from the total synthesis process of being chemical and the manufacturing process complicated and apply to cosmetic, and such method is stable EGCG. Effect very much diminishes in substitution to the alkyl group it can.

#### ※ The Technical Challenges of the Invention

Thus, these inventors solved the above-described EGCG problem in the upper part. EGCG was to the starting material, it was stable. It started to the development of the derivative having the various effect.

In the invention, the nicotinic acids, and, the other efficacy material is used as substituent by reacting EGCG under the presence of 4-dimethylaminopyridine and dicyclohexylcarbodiimide, and the organic solvent with the nicotinic acids. The EGCG derivative having the activity which gives the stability of the extent in which obstacle has no in use to the cosmetic material while keeping, and toxicity has no in the analysis, profitables in vivo tries to be offered.

Moreover, in the invention, the cosmetic composition containing the EGCG derivative tries to be offered.

#### ※ Structure & Operation of the Invention

The invention relates to below chemical formula 1. And it is about the expressed novel EGCG derivative compound.

In the above case, R the nicotinoyl, and the isonicotinoyl or the picolinoyl.

The step that refines the EGCG derivative which first refines in the step : 3) 2) step which first refines by using the organic solvent becomes in the step : 2) 1) step which the nicotinic acids is reacted in 1) organic solvent with EGCG by using dicyclohexyldiimide and dimethylaminopyridine as the coupling agent and produces the EGCG derivative by using the ion-exchange resin is included as to the manufacturing method of the EGCG derivative expressed in the above-described chemical formula 1 offered from the invention.

The manufacturing method of the EGCG derivative according to the present invention can be an idle life led to for example, the following equation 1 :

In the above case, R the nicotinoyl, and the isonicotinoyl or the picolinoyl.

The manufacturing method of the EGCG derivative according to the present invention is same thed more specifically like next.

(1) It is preferable that the nicotinic acids about EGCG in step of manufacturing the EGCG derivative which is expressed to the chemical formula 1 EGCG and nicotinic acids are \*\*\*ed as the coupling agent under the presence of dimethylaminopyridine and dicyclohexyldiimide in the organic solvent in the room temperature 10–20 hours: above statement step it reacts to the equivalence ratio of 1:8~10.4. It is difficult that the number obtained has but the by-product of the excess of quantity gets and it besides refines the intended product 1:10.4 or greater products in which for in only 1:8 U.S., the equivalence ratio, 8 hydroxies is partly substituted for besides the intended product get as by-product. Moreover, it is preferable that EGCG dicyclohexyldiimide it reacts to the equivalence ratio of 1:8~12.4. For in only 1:8 U.S., the equivalence ratio, non-interactant exists. And if 1:12.4 or greater, the by-product of the excess of quantity also becomes and difficulty has in refinement. It is preferable that the dimethylaminopyridine which it together uses as catalyst when using dicyclohexyldiimide as the coupling agent it uses against dicyclohexyldiimide as 0.1 equivalence ratio. In case the EGCG derivative is manufactured with the above-described method, the product in which EGCG and nicotinic acids unite with 1:8 becomes over 61%.

The nicotinic acids used in the invention is known as as the vitamin B3. And many functions is proceed in vivo. The Br. J. Dermatol., and 2000 anti-inflammatory and skin barrier function were increased in the skin in coating reducing the transepidermal water loss, etc it was reported., 143, 524–531).

In the above case, it is preferable that dicyclohexyldiimide, the carbonyl diimidazole, diethylazodicarboxylate etc. can be used as the coupling agent. But dicyclohexyldiimide is used.

In the above case, it is preferable that the latent solvent like the dichloromethane, tetrahydrofurane, the ethyl acetate, acetonitrile, the chloroform, the ethyl ether etc can be used as the organic solvent. But tetrahydrofurane is used.

(2) The reaction solution obtaining the organic solvent from the step of refining the EGCG derivative it uses: (1) step described in the above is filtered and precipitate is eliminated. With making hydrolysis the dicyclohexyldiimide banishing someboby from to the water and exists, impurity is eliminated. After it desiccates in the anhydrous sodium sulfate or the Magnesium Sulfate Anhydrous, solvent is eliminated. Here, after the chloroform being put and warming up, the hexane of the excess of quantity is drops added and the EGCG derivative is segregated, the liquid is eliminated. If the e-process is proceed many times, the EGCG derivative refined to primary can be obtained. Here, it is preferable that the solvent like the dichloromethane, tetrahydrofurane, the ethyl acetate, acetonitrile, the chloroform, the ethyl ether, the hexane, the ethanol, methanol etc can be used as the used organic solvent but the chloroform and hexane are used.

(3) The step of finally refining the EGCG derivative it uses the ion-exchange resin.

By using the ion-exchange resin, the EGCG derivative obtained is refined in (2) step described in the above. Here, the resin used HPTM, SP800TM, SP200TM, Amberlite XADTM, SephadexTM(Diaion) Etc. can be used. It is preferable that the thing which amount of resin uses the treble or greater of the sample amount it desirables. And the various organic solvents can be used as the elution solvent but the acetone and hexane mixture are used.

As material having the effect that prevents the aging of the biological film the production of peroxide is controlled the manufactured EGCG derivative controls the oxidizing action by the active oxygen in the skin in coating at in vivo and the effect promoting the collagen biosynthesis by the manufacturing method, , in addition the magnetic pole about the skin has no the spring plate multiplication of the skin, and prevention and improvement effect of the skin aging have.

In the meantime, it preferably preferables to amount of 0.01~5 weight%, the cosmetic composition multiplies the skin elastic increase and anti-aging effect about the total weight of composition to amount of 0.001~20 weight% as the box.

The cosmetic composition is not limited specially as to the formulation. And formulation including the concrete flexible toilet water, lotion, the massage cream or the moisturizing cream etc. can be had.

Moreover, according to the EGCG derivative comprising the cosmetic composition of the present invention is formulation, the person skilled in the art selects the most fitted without difficulty and it moreover can match according to the intended effect.

Hereinafter, the manufacturing method of the EGCG derivative according to the present invention is explained more specifically through the working example. But the invention is not limited to these working examples.

[Working example 1] The manufacture of the EGCG derivative.

After adding drops the EGCG 4.58 g (10 mmol) after the nicotinic acid 11.8 g (96 mmol), the dicyclohexyldiimide 19.8 g (96 mmol), and the dimethylaminopyridine 1.17 g (9.6 mmol) being put into the tetrahydrofuran 100ml and \*\*\*ing in the room temperature for 30 minutes, it \*\*\*ed 20 hours. After confirming the complete annihilation of reactant, it filtered and precipitate was eliminated. With making hydrolysis the dicyclohexyldiimide in which solution was washed to the water the third and remaining behind, impurity was eliminated. After the organic layer was devided, it dehydrated in the Magnesium Sulfate Anhydrous. Solvent was eliminated after filtering. Here, after the chloroform 50ml was put and product was up warmed, the hexane 150ml was drops added gradually and the EGCG derivative was segregated. The liquid was devided and the dicyclohexylurea of the excess of quantity etc. was eliminated. This process was reiterated more the second and the EGCG derivative was refined first. Here, the EGCG derivative getting was refined to HP20 and pure EGCG derivatives (7.98 g, 61%) were obtained.

FAB-MS (m/z) 1299 (M++1, 3.60), 225 (15.71), 106 (100), 78 (24.77).

[Testing example 1]

After being patch the EGCG derivative of 1% to 120 $\mu$ l 24 hours after Jing MoHa the back region of the guinea pig (Gunea pig), the ultraviolet ray (UVB) 500mJ / cm<sup>2</sup> was examined. The skin was biopsied after ultraviolet irradiation 18 hours. The skin was changed and it separated centrifugal and supernate was used in the injury experiment. The Biochem. Med., and 1976 it was the peroxide lipid the comparison fixed quantity after the fixed quantity of the peroxide lipid reacted the tissue supernatant with 1% Thiobarbituric acid (thiobarbituric acid, TBA), by by using the fluorescence spectrophotometer, the intensity of fluorescence being measured in the activating (excitation) 515nm, and the emission 553nm and using 1,1,3,3- tetraethoxy propane (tetraethoxy propane, TEP) as the standard material, the standard curve was out written.The , 15, and 212-216). experimental result the same like the following table 1.

Material.	Inhibition ratio (%)
Control group.	0
EGCG derivative.	31

## [Testing example 2]

The EGCG derivative of 1% was continued in the hairless mouse as the method for everyday spreading 100 $\mu$ l in forenoon and examining the ultraviolet ray (UVA) of 100 mJ / cm<sup>2</sup> in afternoon 10 daytime. It did not spread the EGCG derivative and as to the control group, only the ultraviolet ray examined. Each group used 10 numbers. By biopsying after 2 moon and using the type 1 pN-collagen, immunostaining was in operation put. Amount of the newly synthesized collagen can be measured by using this dyeing method. Each sample was judged as 5 class to 1 (5 is lowest 1 is the best) and the production rate was obtained (N Engl. J. Med., 1993, 329, 530–535. Eur. J. Biochem., 1983, 134, 183–189). The experimental result thes same like the following table 2.

Material.	Production rate (%)
Control group.	15
EGCG derivative.	35

## [Testing example 3.]The safety of the EGCG derivative.

The safety about the human body above anything else importants because of the raw material of the cosmetic material being used for the human body. This inventor confirmed the raw material after the following experiment as the cosmetic material without toxicity and magnetic pole. The safety test was proceed having the solution made in squalene with 10% concentration.

3–1] acute oral toxicity test (Acute oral toxicity test in mice): as a result of dosing someboby with the EGCG derivative 1ml / kg to the rat of female and male each 5 numbers 10 numbers, the dead animal was not observed and the difference which the weight change after pre-administration took a caution was not observed.

3–2] acute hard husk toxicity experiment ( Acute dermal toxicity test in mice and rabbits): as a result of medicating injectant 1 time and observing 2 daytime general appearance, and the weight change in the rat of female and male each 5 numbers 10 numbers, the dyslipidemia phase was not observed the EGCG derivative 0.2ml / kg in the premedication group. As a result of enforcing to the method for thing same for rabbit, the or more was not observed.

3–3] skin first magnetic pole experiment (Primary skin irritation test): the hair of the back region was eliminated in the rabbit 12 numbers before testing material application 24 hours and it spread in 2.5cm width for 0.1ml 24 hours and it observed. It was adjudged that the observation result magnetic pole had no.

3–4] Eye Irritation Study (Eye irritation test): it diluted in the rabbit 9 numbers to 2% concentration in the saline solution and it dosed someboby with to 0.1ml eye per the animal 1 numbers. The experimental result cornea, the iris, and the special ocular response to stimulus about conjunctiva were not shown.

3–5] skin touch type experiment (Skin sensitization test): the skin disorder symptom including the erythema, edema, incrustation etc. could not observe as a result of enforcing to guinea pig female and male each 3 numbers 6 numbers by the testing method of the Kligman and Magnuson (Magnusson).

3–6] human patch test (Human patch test): according to healthy CTFA guide-line (the Cosmetic Toiletry and Fragrance Association, INC, washington, D. C. 20036, and 1991. reference) against the female 30 people of 20–28 years old, the human patch test was enforced. The result skin primary response to stimulus did not appear.

3–7] accumulation irritant experiment (Repeat Insult Human Patch Test): the accumulation response to stimulus and sensitization response did not appear as a result of doing an experiment to the human patch test object according to the CTFA guide-line.

In the safety test for the skin and toxicity described in the above, the EGCG derivative could confirm material as the external skin preparation safe.

#### [Testing example 4] Stability test.

The stability test the respective 3g. It warmed up in the dimethyl sulfoxide 100ml. The aging was observed between 6 month after safekeeping in 60°C thermostat.

Residual rate.									
Period (month)	1	2	3	4	5	6			
Working example 1.	100	100	97	97	95	95			
EGCG	80	63	50	47	34	12			

Material.	Elapsed time (month)								
1	2	3	4	5	6				
Working example 1.	-	-	-	-	-	+			
EGCG	+	++	++	+++	+++	+++			

Coloring: -: light yellow.

+: the coloring minor.

++: among the coloring.

+++ : coloring part.

#### [Formulation example 1] The creams type.

Component. Capacity (weight%)  
 EGCG derivative.Fluid paraffin.Cetostearylalcohol.Beeswax.Methylpolysiloxane.Oleophilic  
 mono stearin stearate.Stearic acid.Solvitan sesqui oleate.Monostearin acid.Polyoxyethylene  
 sorbitan.Methylparaben.Propylparaben.Perfume.EDTA.2NaGlycerine.Propylene  
 glycol.Triethanolamine.Imidazolidinylurea.Purified water.  
 0.0215.02.03.00.52.02.00.81.01.20.20.10.20.025.05.00.20.3to 100

#### [Formulation example 2] Lotion type.

Component. Capacity (weight%)  
 EGCG derivative.Multi wax.Stearic acid.Fluid paraffin.Di high dag wax.Beewax 17.Nicol MGS-B.Arancel  
 165.Glycerine.Methylparaben.Propylparaben.Liquid paraben.Twin 60.Carbomer.Purified water.  
 0.023.50.55.00.80.051.90.77.00.120.035.00.50.12to 100

#### ■ Effects of the Invention

As illustrated in the above, the EGCG derivative according to the present invention the material which was stable. And the skin photoaging suppression and ultraviolet ray defense effect excellented.



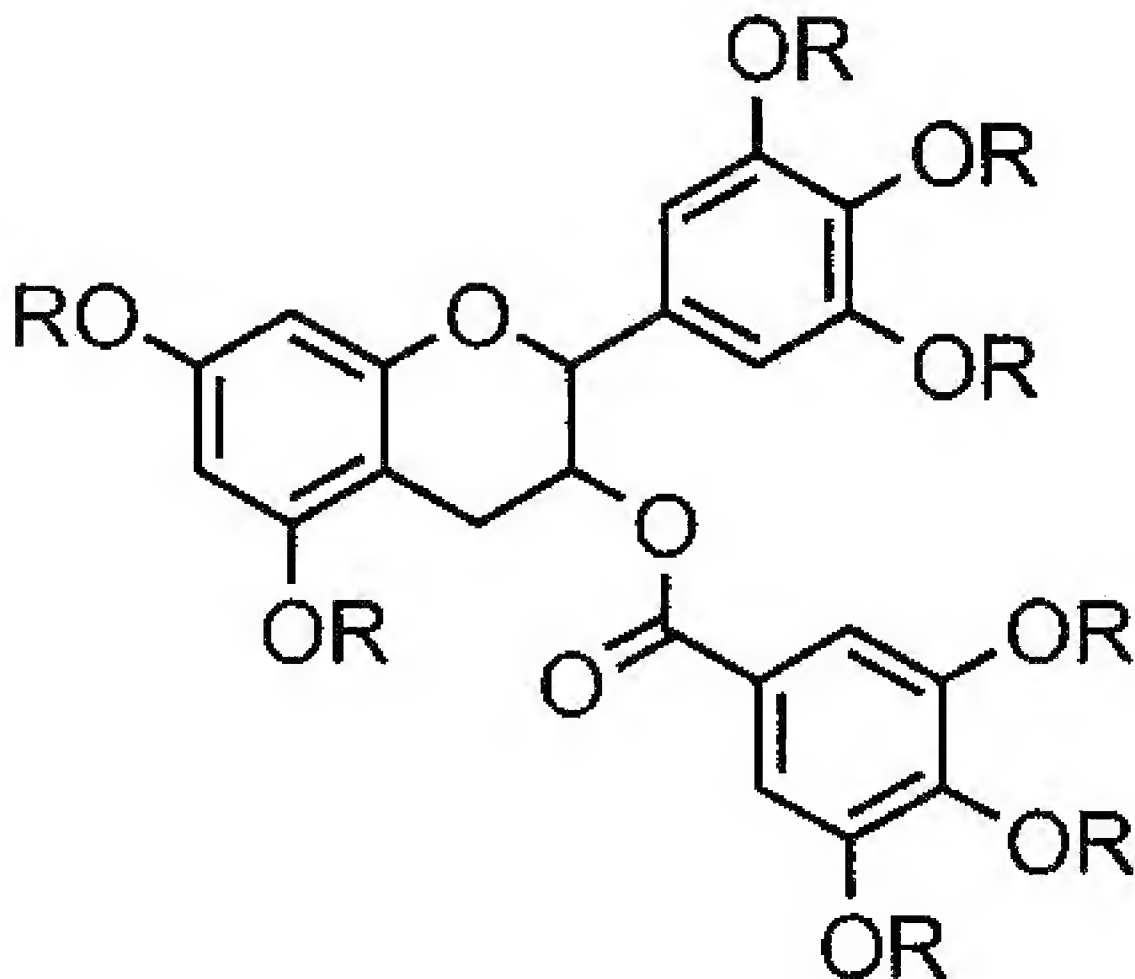
#### Scope of Claims

Claim 1 :

The new EGCG derivative compound expressed in below chemical formula 1 :



[Chemical formula 1]



In the above case, R the nicotinoyl, and the isonicotinoyl or the picolinoyl.

Claim 2 :

1) The method for manufacturing the EGCG derivative that is expressed in the chemical formula 1, method for manufacturing the EGCG derivative comprising: the step that refines the EGCG derivative which first refines in the step : 3) (2) step which first refines separation by using the organic solvent becomes in the step : 2) (1) step which the nicotinic acids is reacted in the organic solvent with EGCG by using dicyclohexyldiimide and dimethylaminopyridine as the coupling agent and produces the EGCG derivative by using the ion-exchange resin.

Claim 3 :

The method for manufacturing the EGCG derivative wherein as to claim 2, the nicotinic acids is the nicotinoyl, and the isonicotinoyl or the picolinoyl.

Claim 4 :

The cosmetic composition wherein the EGCG derivative expressed in the chemical formula 1 in the first claim is about the total weight of composition to amount of 0.001~20 weight%, it.